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DEPARTMENT OF HEALTH & HUMAN SERVICES

New York District

Food & Drug Administration
158-15 Liberty Avenue
Jamaica, NY 11433

January 10, 2008

WARNING LETTER NYK 2008-06

Certified Mail
Return Receipt Requested

Dr. Govind Gil, Owner
American Hormones, Inc.
66 Middlebush Rd., Ste. 300
Wappingers Falls, NY 12590-4047

Dear Dr. Gil:

From December 14 through December 29, 2006, a U.S. Food and Drug Administration (FDA) investigator inspected your firm, American Hormones Inc., located in Wappingers Falls, NY. This inspection revealed that your firm produces human prescription drugs including testosterone lipoderm gel, thyroid (T4/T3) capsules, pregnenolone capsules, DHEA (dehydroepiandrosterone) capsules, and human growth hormone products. During the investigation, our investigator documented serious violations of the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA and FDA's Regulatory Approach to Compounding

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view is that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective" for their labeled uses. *See Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"). There is substantial judicial authority supporting FDA's position that compounded drugs are not exempt from the new drug definition. *See Prof'ls & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug ... provisions, the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding."); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd, Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains

that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.[1]

The drugs that pharmacists compound are rarely FDA-approved and thus lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. *See Thompson v. Western States Medical Center,* 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced drug, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to the compounding of human drugs is articulated in Compliance Policy Guide section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (*see Notice of Availability*, 67 *Fed. Reg.* 39,409 (June 7, 2002)).[2] The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. As stated in the CPG,"[t]he . . . list of factors is not intended to be exhaustive."

B. Factual Background

FDA is seriously concerned about the public health risks associated with the large-scale production of drug products by manufacturers not meeting the laws and regulations applicable to drug manufacturing. Your firm purports to be a compounding pharmacy; however, our investigation

[1] In August 2006, the U.S. District Court for the Western District of Texas issued a ruling in *Medical Center Pharmacy v. Gonzales* interpreting, among other things, the application of the "new drug" provisions of the FDCA to compounded drugs. *See Medical Center Pharmacy v. Gonzales,* MO-04-CV-130, (W.D. Tex, Aug. 30, 2006). The government has appealed this decision to the U.S. Court of Appeals for the Fifth Circuit.

[2] Although section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Ninth Circuit's ruling in *Western States Medical Center v. Shalala,* 238 F.3d 1090 (9th Cir. 2001), that section 503A included unconstitutional restrictions on commercial speech and those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

has determined that your firm's operation exceeds the scope of traditional pharmacy practice. Your firm's activities are not consistent with a pharmacy engaged in extemporaneous compounding, but rather are akin to a pharmaceutical manufacturer.

Compounding Copies and Near Copies of FDA-Approved, Commercially Available Drugs

The inspection disclosed that your firm mass produces several products that are essentially copies of commercially available products, using commercial scale equipment. Specifically, during the period between June 1, 2006, and December 18, 2006, records indicate that your firm manufactured and dispensed high volumes of the following products:

- Thyroid (T4/T3) 1 Grain (60 mg) Capsules -- [redacted] lots, ranging from [redacted] to [redacted] capsules, were made with a total of [redacted] capsules produced.
- Testosterone Lipoderm 50 mg/ml Gel -- [redacted] grams were produced in [redacted] different lots.
- Testosterone Lipoderm 100 mg/ml Gel -- [redacted] lots, all [redacted] grams in size, were made for a total of [redacted] grams.

The Thyroid (T4/T3) 1 Grain (60mg) Capsule and the Testosterone Lipoderm 50 mg/ml gel products are copies or near copies of FDA-approved drug products and appear to be compounded without a medical need for their variation from the FDA-approved, commercially-available drugs with which they compete. We also found that your firm appears to anticipatorily compound large volumes of these drugs, in batches produced three to six weeks in advance of dispensing.

The Testosterone Lipoderm 50 mg/ml gel product compounded by your firm is a copy or essentially a copy of an FDA-approved product. Your supervising pharmacist claims that your products differ from the FDA-approved products because lipoderm is used as a base to improve consistency and effectiveness. However, for the purpose of exercising our enforcement discretion, we do not view the use of this lipoderm base to be a meaningful distinction between your product and the FDA-approved product with which it competes. Nor are we aware of any legitimate medical need for a lipoderm-based product. As noted above, FDA will generally not exercise enforcement discretion for such compounded drugs.

Likewise, the compounded Thyroid (T4/T3) 1 Grain (60 mg) Capsule product distributed by your firm is a copy or essentially a copy of an FDA-approved Thyroid (T4/T3) 60 mg tablet product. Your supervising pharmacist claims that your product differs from the commercially available product in that the ingredients T3 and T4 are from synthetic laboratory sources rather than natural sources and the dosage form is a capsule and not a tablet. However, for the purpose of exercising our enforcement discretion, we do not view the use of the same ingredients from synthetic laboratory sources, or the difference in dosage form, to be a meaningful distinction between your product and the FDA-approved product with which it competes. Nor are we aware of any legitimate medical

need for the variation in your product from capsule to tablet.

FDA's findings regarding your firm's testosterone and thyroid products are particularly troubling because your firm produces these products in large volume. We also note that your firm produced a large volume of Testosterone Lipoderm 100 mg/ml Gel. For example, your firm produced [redacted] lots of the product between May and November, 2006, with each lot [redacted] grams in size, for a total of [redacted] grams. We will not exercise enforcement discretion toward your firm's continued production of these drugs that are copies or essentially copies of FDA-approved drugs where there is no legitimate medical need for the variations from their corresponding FDA-approved products.

Products Using Active Ingredients that Are Not Components of Approved Drug Products

In addition, the inspection disclosed that your firm makes products from bulk substances that are not components of FDA-approved drugs. Your records show that your firm produces Pregnenolone SR 100 mg capsules and DHEA (Dehydroepiandrosterone) SR 15mg capsules products. Your firm also compounds hormone therapy products containing Estriol.

Pregnenolone, DHEA, and Estriol are not active ingredients contained in any FDA-approved drug. FDA does not sanction their use in pharmacy compounding and will not exercise enforcement discretion with respect to products that contain Pregnenolone, DHEA, or Estriol.

C. Violations of the FDCA

Unapproved New Drugs

In light of the above discussion, FDA will not exercise enforcement discretion for the testosterone gel, thyroid capsules, pregnenolone capsules, DHEA capsules, and hormone therapy products containing Estriol manufactured by your firm.

Your firm compounds each of these products without an FDA-approved new drug application or an FDA-sanctioned investigational new drug application. Because your products are intended to treat, mitigate, and/or prevent disease, the products are drugs within the meaning of section 201(g) of the FDCA [21 U.S.C. § 321(g)]. Further, as these products are not generally recognized by qualified experts as safe and effective for their labeled uses, they are new drugs, as defined by section 201(p) of the FDCA [21 U.S.C.§ 321(p)]. They may not be introduced or delivered for introduction into interstate commerce under section 505 of the FDCA [21 U.S.C. § 355] because no approval of an application filed pursuant to section 505(b) or (j) of the FDCA [21 U.S.C. §§ 355(b), (j)] is in effect for them. Their introduction or delivery for introduction into interstate commerce violates section 505(a) of the FDCA [21 U.S.C. § 355(a)].

In addition, these drugs are misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] in that their labeling fails to bear adequate directions for their use, and they are not exempt from this requirement under 21 CFR § 201.115, and do not otherwise comply with section 505(i) of the FDCA [21 U.S.C. § 355(i)]. Section 301(k) of the FDCA [21 U.S.C. § 331(k)] prohibits any act with respect to a drug if the act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded. Further, section 301(a) of the FDCA [21 U.S.C. § 331(a)] prohibits the introduction or delivery for introduction into interstate commerce of any misbranded drug.

Adulterated Drugs

As discussed below, our inspection revealed that your firm engages in activities that fall outside the traditional practice of pharmacy compounding and is instead more representative of a drug manufacturer.

Therefore, your drug products are adulterated under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)] because the controls and procedures used in their manufacture, processing, packing, and holding do not conform to current good manufacturing practice regulations, 21 CFR Parts 210 and 211. Deviations from these regulations include, but are not limited to the following:

1. Failure to have a written testing program designed to assess the stability characteristics of drug products and test data to support an appropriate expiration date for drug products [21 CFR §§ 211.166(a) and (b)]. The firm assigns a 6-month expiration date to all the drug products without providing supporting documentation or the rationale underlying its decision.

2. Failure to assure batch uniformity and integrity of in-process materials and drug products by monitoring the output of those manufacturing processes that may cause variability in drug products [21 CFR § 211.110]. In-process checks including capsule weight variation and adequacy of mixing, to ensure that all ingredients are blended to achieve a homogeneous mixture, are not performed.

3. Failure to establish written procedures for the cleaning and maintenance of equipment, including utensils used in the manufacture, processing, packing, and holding of a drug product [21 CFR § 211.67(a) and (b)]. The firm did not provide evidence to demonstrate that the current practice of cleaning the non-dedicated equipment with alcohol is sufficient to prevent contamination of the drug product. This equipment is used to manufacture several drugs with many formulations.

4. Failure to test each batch of drug product for satisfactory conformance to final specifications including the identity and strength of each active ingredient prior to release [21 CFR § 211.165(a)].

5. Failure to have written procedures for production and process controls designed to assure that drug products have the identity, strength, quality, and purity that they purport or are represented to possess [21 CFR § 211.100]. For example, you have not established critical control and process parameters for any of your drug products nor have you performed performance qualification on equipment used in manufacturing these drug products. Therefore, there is no assurance that you can manufacture drug products in a reliable and reproducible manner.

6. Failure to test each component for conformity with all appropriate written specifications, or failure to perform an identity test and to verify the reliability of the supplier's report of analysis [21 CFR § 211.84(d)(2)]. For components accompanied by a certificate of analysis (COA), no identity test is performed and no verification of the supplier's test results is completed. In the absence of a COA, the firm has failed to test each component against all appropriate specifications.

7. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR § 211.198(a)].

Misbranded Drugs

For the reasons described below, your hormone therapy products containing Estriol are misbranded. Under section 502(a) of the FDCA, a drug is misbranded if its labeling is false or misleading in any particular. Section 201(n) of the FDCA [21 U.S.C. § 321(n)] provides that, in determining whether a drug's labeling or advertising "is misleading, there shall be taken into account . . . not only representations made or suggested . . . but also the extent to which the labeling or advertising . . . fails to reveal facts material in light of such representations . . . ."

Your website advises that you compound hormone therapy drugs containing Estriol that are available for purchase and distribution. These compounded hormone therapy drugs are misbranded within the meaning of section 502(a) of the FDCA for the following reasons:

1. *Unsubstantiated Efficacy Claims*

Your firm's website contains claims concerning your firm's compounded hormone therapy drugs, including:

- "Studies show Micronized Bio-identical Estrogens May Protect Against:
  - Strokes
  - Alzheimer's disease"
- "Studies show Micronized Bio-identical Progesterone May Protect Against:
  - Uterine Cancer
  - Breast Cancer
  - Fibrocystic disease"

- "Progesterone is effective for mood changes and depression."

FDA regards these claims as false and misleading. FDA is not aware of substantial evidence (consisting of adequate and well controlled clinical investigations) that supports these claims.

2. *Unsubstantiated Superiority Claims*

Your firm's website contains statements suggesting the superiority of your firm's compounded hormone therapy drugs:

- "Synthetic hormones are not a perfect match in the body; they try to trick the body. A bio-identical hormone does not have to trick the body. Synthetic hormones produce abnormal metabolites that may also cause side effects and increase the cancer risk."
- "Bio-Identical progesterone allows women to feel much better than they do on any of the synthetic progestins with none of the side effects of synthetic products . . . ."
- "You need hormones, but you need the correct kind, the natural bio-identical hormones, in the correct balance. Don't tolerate the risks of the synthetic hormones when a safer alternative is available.

These statements represent and suggest that your firm's compounded hormone therapy drugs are superior to other hormone therapy products, including FDA-approved drugs. These claims – which are unsupported by substantial evidence (consisting of adequate and well controlled clinical investigations) -- are false and misleading.

3. *Unsubstantiated "Bio-identical" Claims*

Your website claims that your firm's compounded hormone therapy drugs are "bio-identical." This claim implies that your compounded hormone therapy drugs are natural, or identical to the hormones made by the body. FDA is unaware of substantial evidence (consisting of adequate and well controlled clinical investigations) to support the claimed "bio-identical" nature of your hormone therapy drugs.

As explained above, the claims made for your hormone therapy drugs are false and misleading in that they are not supported by substantial evidence. These claims cause your hormone therapy drugs to be misbranded under section 502(a) of the FDCA.

Failure to Register as a Manufacturer and List Drug Products

Your firm's operation exceeds the scope of a traditional pharmacy that regularly engages in dispensing prescription drugs upon receiving a prescription from a practitioner licensed to administer such drugs to patients under the care of such practitioner in the course of its professional practice.

Thus, your firm is subject to the registration and listing requirements under section 502(o) of the Act [21 U.S.C. § 352(o)], and must comply with those requirements.

Failure to comply with these requirements causes your products to be misbranded as they are manufactured in an establishment not duly registered under section 510 of the Act [21 U.S.C. § 360], and the drugs have not been listed as required by section 510(j) of the Act [21 U.S.C. § 360(j)].

The above violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the FDCA and its regulations. Other federal agencies may take this Warning Letter into account when considering the award of contracts.

You should take prompt action to correct the violations cited in this letter and to assure that such violations do not recur. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction.

During the inspection, it appears from your prescription logs that your firm compounds human growth hormone products. For your information, 21 U.S.C. § 333(e) states that, "whoever knowingly distributes, or possesses with the intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under 21 U.S.C. 355 and pursuant to the order of a physician, is guilty by not more than 5 years in prison, such fines are authorized by Title 18, United States Code, or both." Compounding human growth hormone for anti-aging treatment or any other unapproved use would violate 21 U.S.C. § 333(e).

We are also concerned that you are placing a six-month expiration date on products dispensed without scientific evidence of the validity of these dates. Labeling these products with this expiration date may pose a risk to health.

We acknowledge receipt of a letter on your behalf dated January 26, 2007, from the law firm of Geller & Klein, P.C. We do not agree with the letter's assessment that American Hormones is not subject to FDA inspection. Under the FDCA, FDA has the authority to inspect any factory, warehouse, or establishment (including any pharmacy) in which drugs are manufactured, processed, packed, or held for introduction into interstate commerce. 21 U.S.C. § 374. FDA's inspection authority with respect to such establishments (including any pharmacy) also extends to written records and files. 21 U.S.C. § 374(a)(1).

Under 21 U.S.C. § 374(a)(2)(A), licensed pharmacies are exempt from records inspection only if their practices comply with local laws, they dispense prescription drugs pursuant to a valid prescription, and they do not prepare drugs outside the traditional scope of a retail pharmacy business. In determining whether this statutory exemption applies, FDA may rely on its CPGs "as a reasonable basis upon which to initiate inspection under the FDCA." See Wedgewood Village Pharmacy v. United States, 421 F.3d 263, 273 (3d Cir. 2005). Your firm prepares drugs outside the

traditional scope of a retail pharmacy business, because it prepares copies or near-copies of commercially available drug products in large volumes. Under its CPGs, these are among the factors the agency takes into account in determining whether an establishment is operating outside of the traditional practice of pharmacy. Thus, based on these findings, FDA reasonably concluded that your firm does not meet the criteria of the section 374(a)(2)(A) exemption and its facility is subject to FDA inspection under section 374(a)(1), including records inspection under the third sentence of that provision.

We note that the letter does not dispute that your firm uses equipment of greater capacity than equipment used by other compounders. The reason presented is the "quantity of mixes and volume of demand handled by American Hormones." The letter asserts that the equipment used is "far beneath commercial scale." We disagree. FDA's investigators found equipment on premises capable of producing large quantities of drug products. These include a [redacted] blender and an electric mixer each with a [redacted] kilogram capacity, and an encapsulation machine capable of producing [redacted] capsules each production run.

Please notify this office in writing, within fifteen working days of receipt of this letter, of the action that you will take to correct the violations cited above, including an explanation of the steps taken to prevent their recurrence. You should include in your response documentation, such as procedures or other useful materials, to assist us in evaluating your corrective action. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be complete. You can find guidance and information regarding regulations through links at FDA's Internet website at http://www.fda.gov.oc.industry.

Address your reply to the attention of Richard T. Trainor, Compliance Officer, U.S. Food and Drug Administration, 300 Hamilton Ave., White Plains, New York 10601, telephone number 914-682-6166 x34.

Sincerely,

Otto D. Vitillo

Otto D. Vitillo
District Director